

REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated October 24, 2006 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

I. Amendments

Claims 1 and 26 are amended to recite correlating a change in membrane fluidity to binding. Basis for these amendments can be found at least on page 14, lines 13-16 and lines 33-34.

Claim 4 and 29 are amended to recite the label is attached to one or more of the lipid bilayer expanses.

Claims 36 and 39 are amended to remove "a plasma membrane vesicle."

No new matter is added by way of these amendments.

II. Interview Summary in accord with MPEP § 713.04

1. The applicants thank Examiners Foster and Le for granting a telephonic interview regarding the above-referenced application on March 13, 2007. The participants were Examiner Foster (USPTO), Examiner Le (USPTO), Jacqueline Mahoney (Applicant's representative), Judy Mohr (Applicant's representative), Jay Groves (inventor), and Jeremy Blitzer (Applicant representative). This written summary is submitted in accordance with MPEP §713.04.

2. No exhibits were shown or discussed.
3. Claims 1 and 26 were discussed.
4. Boxer *et al.* (US 6,228,326 and WO 98/23948) and Keinanen *et al.* (US 6,235,535) were discussed.
5. Requirements for overcoming the outstanding Written Description, Enablement, and obviousness rejections were discussed.
6. An agreement was not reached.

III. Rejections under 35 U.S.C. §112, first paragraph

Claim 36 was rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement.

Claims 1-7, 10, 34-36, and 40 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claims 1-7, 10, 34-36, and 40 were further rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most connected to make and use the invention commensurate in scope with the claims.

A. Written Description

1. Claim 36

Claim 36 was rejected for the language "a plasma membrane vesicle." Applicants have amended claims 36 and 39 to remove reference to "a plasma membrane vesicle" as this subject matter is already encompassed by the claimed "vesicle."

2. Claims 1-7, 10, 34-36, and 40

The Examiner asserts that the specification fails to provide an adequate written description of the invention as claimed. The claims, as amended, are directed to an assay method for determining binding of a test agent and a lipid-bilayer-associated component associated with a lipid bilayer expanse of the array device. The membrane fluidity of one or more of the lipid expanses is changed by this binding. The membrane fluidity is evaluated and binding of the test agent and the lipid bilayer-associated component is correlated to a change in membrane fluidity.

As noted above, the present method comprises the steps of (i) providing a surface detector array device, (ii) contacting the device with a bulk aqueous phase comprising a test agent, whereby the membrane fluidity of one or more lipid bilayer expanses changes when the test agent binds to the lipid bilayer-associated

component, and (iii) evaluating the membrane fluidity of one or more of the lipid bilayer expanses.

With regard to step (i), surface detector array devices are described on page 9, lines 15-31 and an exemplary device is shown in Fig. 1.

With regard to (ii), contacting the device with a bulk aqueous phase comprising a test agent and detecting the binding of the test agent to the lipid bilayer-associated component through their effects on the membrane fluidity of the lipid bilayer is described on page 14, line 8. Methods for measuring and evaluating the membrane fluidity are described on page 14, line 19 through page 15, line 15.

The Examiner states that there is no disclosure of the claimed genera of test agents and lipid bilayer-associated components beyond the disclosure of cholera toxin subunit B (CTB) and ganglioside GM1. Applicants respectfully remind the Examiner that the claimed method is an assay for determining binding. The purpose of the assay is to determine binding. Therefore, Applicants should not need to show test agents and lipid-bilayer-associated components to which they know will bind. Applicants have shown that binding of a test agent to a lipid bilayer-associated component does effect a change in the membrane fluidity (Example 6).

Examiner Foster invited Applicants to submit publications showing that other test agents cause a change in membrane fluidity when bound. In addition to the several articles discussed by the Examiner, Applicants submit seven articles herewith demonstrating the effects of diverse small molecules and peptides on membrane fluidity:

Carrier et al., Biochemical Pharmacology, 53:401-408, 1997.

Hashimoto et al., Journal of Lipid Research, 42:1160-1168, 2001.

Kremer et al., Biochemistry, 39:10309-10318, 2000.

Ohyashiki et al., J. Biochem., 111:419-423, 1992.

Pezeshk et al., Life Sciences, 63:1863-1870, 1998.

Tsuchiya et al., Clinical and Experimental Pharmacology and Physiology, 28:292-299, 2001.

Abu-Salah, Biochemical Pharmacology, 42:1947-1951, 1991.

As shown in these references, small molecules and short peptides with vastly different structures, functional properties, and applications all have measurable effects on the membrane fluidity. These molecules represent a fair sampling of the universe of possible test agents which may be encountered during the drug screening process, which is one important application of this invention.

Specifically, the effects were:

1. amyloid-beta (39-40 amino acid peptide) decreases fluidity;
2. daunomycin (a chemotherapeutic agent) decreases fluidity;
3. amikacin (antibiotic) decreases fluidity;
4. kanamycin A and B (antibiotics) decreases fluidity;
5. propofol (sedative) increases fluidity;
6. docosahexenoic acid (fatty acid present in membranes) increases fluidity;
7. malondialdehyde (lipid degradation product) decreases fluidity;
8. amphotericin B (antifungal agent) increases fluidity;
9. nystatin (antifungal agent) increases fluidity;
10. valinomycin (peptide antibiotic) decreases fluidity;
11. gramicidin A (peptide antibiotic) decreases fluidity;
12. procaine (local anesthetic) decreases fluidity.

An exemplary, and potentially important, use of the claimed method is in screening of large libraries of compounds as potential therapeutic agents. Binding of potential agents to a lipid bilayer component is an indicator of therapeutic activity.

Finally, the Examiner is directed to Example 12 of the USPTO Written Description Guidelines. Recognizing that the scenario is a computer implemented method, the case is analogous to the present method in that both are directed to determining a result by detecting an interaction. In accord with the Guideline scenario, providing a surface detector array device was known in the art as evidenced by U.S. Patent No. 6,228,326 and methods for evaluating membrane fluidity are known in the art. Further, the present specification provides guidance for evaluating the membrane fluidity. In contrast to the Guideline scenario, the

present application provides an actual reduction to practice as well as a clear depiction of the claimed assay.

3. Claim 3

With regard to claim 3, the Examiner states that there is no written description of a method for detecting the interaction of a test agent with bilayer-associated bacterial endotoxin and cites Examples 3-4, and 6 where CTB is the test agent. The prototypical example of an endotoxin is lipopolysaccharide (LPS) or lipo-oligo-saccharide (LOS) that is part of the outer membrane of the cell wall of Gram-negative bacteria. CTB, however, is an exotoxin - a protein secreted by the bacterium. Unlike an exotoxin, an endotoxin is not secreted in soluble form, but is a structural component. The disclosure, on page 31, lines 31-32, clearly states that the endotoxin is displayed as an array element – that is the lipid bilayer-associated component.

In view of the teachings in the specification, the level of skill, and the knowledge in the art, one skilled in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the invention was filed.

B. Enablement

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention without undue experimentation (e.g., *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The enablement requirement is met if the description enables any mode of making and using the claimed invention (*Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 20 USPQ2d 1300 (Fed. Cir. 1991).

As noted above, the amended claims are directed to a method for assaying an interaction between a test agent and a lipid bilayer-associated component using a surface detector array device including a plurality of lipid bilayer expanses. When

the test agent binds to the lipid bilayer-associated component, the membrane fluidity of the lipid bilayer expanse(s) is changed. Example 7 of the present invention provides guidance for an exemplary test agent and lipid bilayer-associated component, specifically the cholera toxin and the ganglioside GM1 membrane target. Applicants have noted above literature support for twelve further small molecules/peptides that cause a change in fluidity upon interacting with the cell membrane.

The Examiner noted that "the prior art teaches that integral membrane proteins in supported bilayers may often be non-functional, and therefore incapable of interacting with test agents" (Office action page 10). While this may be true, the same reference cited by the Examiner lists a number of standard methods known in the art to enhance the activity of integral membrane proteins. One exemplary method relies on the use of polyethylene glycol cushions to enhance the mobility and activity of integral membrane proteins (Wagner ML and Tamm L (2000) *Biophys J*, 79: 1400-1414).

In determining enablement, the courts have identified several Wands factors to be considered:

(i) The nature of the invention and (ii) breadth of the claims: Claim 1 as amended relates to a method for assaying an interaction between a test agent and a lipid bilayer-associated component. The method comprises (i) providing a surface detector array device comprising; (ii) contacting the device with a bulk aqueous phase comprising the test agent that specifically binds to the lipid bilayer-associated component, whereby the membrane fluidity of at least one of the plurality of lipid bilayer expanses changes when the test agent binds to the lipid bilayer-associated component; (iii) evaluating the membrane fluidity of one or more of lipid bilayer expanses, and (iv) detecting binding of the test agent to the lipid bilayer-associated component by correlating a change in membrane fluidity to binding.

(iii) The state of the prior art and (iv) the predictability of the art: At the time of the invention, a surface detector array device was known as evidenced by U.S.

Patent No. 6,228,326. Further, methods for evaluating membrane fluidity were known in the art as also known from the '326 patent.

(v) The amount of direction or guidance presented and (vi) the presence or absence of working examples: Evaluating membrane fluidity is known in the art and described in the specification page 14, line 19 through page 15, line 15. Example 6 in the application provides working details to conduct such tests.

(vii) The quantity of experimentation necessary: The present method is directed to assaying an interaction between a test agent and a lipid bilayer associated component. The present application provides ample guidance for any experimentation necessary in the present method.

Accordingly, Applicants submit that the specification would enable any person skilled in the art to which it pertains to make and use the claimed invention.

In light of the above, Applicants submit that the present claims satisfy the requirements of 35 U.S.C. §112, first paragraph and respectfully request that the rejections be withdrawn.

IV. Rejection under 35 U.S.C. §112, second paragraph

Claims 4-7 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claim 4 is amended to recite that the label is attached to one or more of the lipid bilayer expanses.

In light of the above amendments, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

V. Rejections under 35 U.S.C. §103

Claims 1-2, 4-7, 10, 34-36, 40, and 42 were rejected under 35 U.S.C. §103 as allegedly obvious over Boxer *et al.* (U.S. 6,228,326 patent), or, alternatively, Boxer *et al.* (PCT Publication No. WO 98/23948) in view of Keinanen *et al.* (U.S. Patent No. 6,235,535).

Claim 3 was rejected under 35 U.S.C. §103 as allegedly obvious over Boxer *et al.* (the '326 patent), or, alternatively, Boxer *et al.* (PCT Publication No. WO 98/23948) in view of Keinanen *et al.*, and further in view of Gutzmann *et al.* (Biophysical Journal, 80:2935-2945, 2001).

These rejections are respectfully traversed.

A. The Present Claims

The present method as embodied by claim 1 comprises a method for assaying an interaction between a test agent and a lipid bilayer-associated component. The method comprises (i) providing a surface detector array device comprising (a) a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions, (b) a plurality of lipid bilayer expanses localized above the plurality of distinct bilayer-compatible surface regions, the lipid bilayer expanses having a component associated with the lipid bilayer expanse; (ii) contacting the device with a bulk aqueous phase comprising a test agent that specifically binds to the lipid bilayer-associated component, whereby the membrane fluidity of at least one of the plurality of lipid bilayer expanses changes when said test agent binds to said lipid bilayer-associated component; (iv) evaluating the membrane fluidity of one or more of the lipid bilayer expanses, and detecting binding of the test agent to the lipid bilayer-associated component by correlating a change in membrane fluidity to binding.

B. The Cited References

BOXER ET AL., THE '326 PATENT relate to a surface detector array device, comprising (i) a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions, (ii) a lipid bilayer expanse stably localized on each of said bilayer-compatible surface regions, (iii) an aqueous film interposed between each bilayer-compatible surface region and corresponding lipid bilayer expanse, wherein each lipid bilayer expanse

is stably localized above each bilayer-compatible surface, and (iv) a bulk aqueous phase covering the lipid bilayer expanses.

BOXER ET AL., THE '948 PUBLICATION corresponds to the '326 patent for purposes of the Examiner's rejections and is thus, not separately discussed.

KEINANEN ET AL. relate to a fluorescence-based immunoassay method for the detection of an analyte. The method includes attaching receptor molecules to a lipid membrane, contacting a sample with the receptor molecules, and measuring the fluorescence change caused by a change of aggregation level of the receptor molecules.

GUTSMANN ET AL. investigate the relationship between the interaction of CAP-18-derived peptides with membranes and the activity of the peptides.

C. Analysis

According to the M.P.E.P. § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

1. Rejection of claims 1-2, 4-7, 10, 34-36, 40, and 42

The combination of Boxer *et al.* and Keinanen *et al.* fail to teach a method for assaying an interaction between a test agent and a lipid bilayer-associated component including evaluating the membrane fluidity of one or more of the lipid bilayer expanses and detecting binding of the test agent to the lipid bilayer-associated component by correlating a change in membrane fluidity to binding. As noted by the Examiner, the Boxer *et al.* references fail to specifically teach evaluating membrane fluidity in order to detect binding between a test agent and a lipid bilayer-associated component. Keinanen *et al.* is cited for a teaching of

"microaggregation" or "aggregation level." Keinanen *et al.* does not, in fact, measure membrane fluidity, but instead measures direct binding. Although Keinanen *et al.* measures aggregation of membrane receptors (e.g. antibodies), this cannot be correlated with fluidity of the membrane itself. Indeed, the membrane could have no fluidity and one could still measure the aggregation of receptors in the membrane. In fact, the FRET method as described in Keinanen *et al.* cannot determine membrane fluidity. Keinanen *et al.* teach one population of a lipid-tagged antibody labeled with a donor fluorophore and a second population of a lipid-tagged antibody labeled with an acceptor fluorophore. When a multivalent antigen binds the antibodies, the FRET phenomenon occurs. As both the labels are bound to the lipid bilayer-associated component (the lipid-linked antibody in this case), a change in FRET can only be interpreted as a self-association of the antibodies. Hence, what is being measured in Keinanen *et al.* is a change in the interaction of the membrane-anchored antibodies; not a change in the overall fluidity of the membrane itself.

2. Rejection of claim 3

The deficiencies of the '326 patent and Keinanen *et al.* are described above. Nor does Gutsmann *et al.* provide the missing teaching. Instead, Gutsmann *et al.* describe several biophysical techniques to investigate the interaction of CAP-18 peptides and a membrane but make no mention of evaluating the fluidity of the membrane.

As the references, alone or in combination, fail to teach or suggest all the claim limitations, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

VI. Obviousness-Type Double Patenting Rejections

Claims 1-2, 4-7, 10, 34-36, 40, and 42 were rejected under the judicially created doctrine of obviousness-type double patenting as being directed to an invention not patentably distinct from claims 22-26 of co-owned patent no. 6,699,719 in view of Keinanen *et al.*

A. The Present Claims

The present application comprises a method for assaying an interaction between a test agent and a lipid bilayer-associated component. The method comprises (i) providing a surface detector array device comprising (a) a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions, (b) a plurality of lipid bilayer expanses localized above the plurality of distinct bilayer-compatible surface regions, the lipid bilayer expanses having a component associated with the lipid bilayer expanse; (iii) contacting the device with a bulk aqueous phase comprising a test agent that specifically binds to the lipid bilayer-associated component, whereby the membrane fluidity of at least one of the plurality of lipid bilayer expanses changes when said test agent binds to said lipid bilayer-associated component; (iv) evaluating the membrane fluidity of one or more of the lipid bilayer expanses, and detecting binding of the test agent to the lipid bilayer-associated component by correlating a change in membrane fluidity to binding.

B. U.S. Patent No. 6,699,719 (the '719 patent)

The '719 patent relates to a multiplexed assay, comprising the steps of:

(i) providing a surface detection array device, said device comprising a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions, said bilayer-compatible surface regions and said bilayer barrier regions being formed of different materials, a first lipid bilayer expanse having a first composition and stably localized above a first of said plurality of distinct bilayer-compatible surface regions, a second lipid

bilayer expanse having a second composition different from said first composition and stably localized above a second of said plurality of distinct bilayer-compatible surface regions, wherein each of said expanses is localized above each of said surface regions in the absence of covalent linkages between each of said lipid bilayer expanses and each of said bilayer-compatible surface regions, and is separated therefrom by an aqueous film interposed between said bilayer-compatible surface regions and said corresponding lipid bilayer expanses;

(ii) contacting said device with a bulk aqueous phase comprising a test agent; and

(iii) assaying an interaction between said test agent and said first composition and an interaction between said test agent and said second composition.

C. Analysis

The purpose of obviousness-type double patenting is to prevent improper timewise extension of patent rights by prohibiting the issuance of claims in a second application which are not "patentably distinct" from the claims of the first patent. M.P.E.P. 804(II)(B)

The present method requires a step of evaluating the membrane fluidity of one or more of the lipid bilayer expanses and detecting binding of the test agent to the lipid bilayer-associated component by correlating a change in membrane fluidity to binding. Thus, the present method evaluates a membrane property, namely membrane fluidity, in order to assay the interaction of the test agent and the lipid bilayer-associated component. This feature is not an obvious variation of the "assaying an interaction between said test agent and said first composition and an interaction between said test agent and said second composition."

Accordingly, Applicants respectfully request withdrawal of the obviousness-type double patenting rejections.

VII. Conclusion

Applicants respectfully submit that the pending claims are in condition for immediate allowance. The undersigned invites the Examiner to call (650) 838-4410 with any questions or comments. The Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-2207.

Respectfully submitted,
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